

REMARKS

Claims 1-10 and 21-32 were pending in the present application.

Applicants have amended, without prejudice, claims 1, 21, and 31 to clarify that which Applicants regard as the invention. Specifically, claims 1, 21 and 31 have been amended to remove the term "about" in the pH range.

New claims 37-42 are directed to embodiments where the buffer is within a pH range of 6.4 to 7.4, and, in claims 38, 40 and 42, also has a chlorobutanol concentration from 0.4% to 0.6% (w/v). Support for these amendments can be found in the specification (as published as U.S. Patent Application Publication No. US 2007/0148765 A1), for example, in paragraphs [0025] (chlorobutanol concentration) and [0029] (pH range).

Applicants respectfully submit that no new matter has been added by these amendments.

After entry of the amendments, claims 1-10, 21-32, and 37-42 will be pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Claim Rejections – 35 USC § 103

Claims 1, 2, 9, 10, 21, 22, and 29-32 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao et al. (WO 01/40455; "Gao"). The Examiner maintains that it would be obvious to one of ordinary skill in the art and well within the ability of the ordinary artisan to use an amount of chlorobutanol that is effective for the purpose of preservation, and to determine a suitable buffer and pH for the composition. The Examiner further maintains that it would have been obvious to use a vial to store the contents of the formulation in order to contain and protect the formulation for delivery, storage and subsequent use.

In response to Applicants' arguments presented in an Amendment under 37 C.F.R. § 1.114 filed on November 13, 2009 ("November 2009 Amendment"), the Examiner (1) noted that the claims encompass a buffer having a pH range of about 6.0 to about 9.0 and do not exclude a pH below 6.0; and (2) asserts that the unexpected results seen with A195 in combination with chlorobutanol appear to be particular to these specific conditions since other formulations do not appear to have had the unexpected result.

In response to (1), Applicants have amended the claims to specify that the buffer has a pH range of 6.0 to 9.0 by removing the term "about". As the claims now exclude a pH below 6.0, Applicants respectfully submit that the amended claims are patentable over Gao.

Applicants also note that newly added claims 37-42 are directed, *inter alia*, to a buffer having a pH within a pH range of 6.4 to 7.8.

In response to (2), Applicants respectfully submit that a *prima facie* case of obviousness based on overlapping ranges can be rebutted by either (i) showing the prior art teaches away from the invention or (ii) showing there are unexpected results over the prior art. See MPEP § 2144.05.

As discussed in the November 2009 Amendment, the Taub (Taub *et al.*, 1943, J. Amer. Pharm. Assoc. 32:28-31) and Patwa (Patwa *et al.*, 1966, J. Amer. Pharm. Assoc. NS6:372-373) references teach that chlorobutanol is not stable in buffered solutions greater than pH 6. This, in itself, is sufficient to show the art teaches away from using chlorobutanol as a preservative in buffered formulations with a pH greater than 6.

The Examiner pointed out that the Akers (Pharm. Technol. May 1984, pp. 36-46) reference, in showing that chlorobutanol was not effective as a preservative at a pH of 5 or greater, was not clear if the chlorobutanol solution was buffered. Applicants respectfully submit that for the lower limit of the pH range in question, i.e., pH 6.0, it does not matter if the solution was buffered or unbuffered. The preservative effect of chlorobutanol is directed related to its stability in solution. See, e.g., Taub. first paragraph of the Summary. Taub teaches that chlorobutanol may be used in buffered solutions up to pH 6 and in unbuffered solutions between pH 3 - 9. See Taub, conclusion numbers 2-4 and second paragraph of the summary. Similarly, Patwa teaches that chlorobutanol may be used with and without buffer at pH 5 to 6. See Patwa, summary and conclusion. Thus, it is irrelevant whether the chlorobutanol solution in Akers was buffered or unbuffered. The skilled artisan would conclude from Table IV of Akers that chlorobutanol would not be an effective preservative at a pH from 5 to 6 (as well as at higher pH). This demonstrates that the art teaches away from using chlorobutanol as a preservative in formulations having a pH in a pH range from 5 to 6.

While Applicants believe unexpected results are not necessary to provide further support for rebutting the obviousness of the ranges, Applicants respectfully submit the unexpected results (in terms of antimicrobial activity) seen with formulation A195 at pH 6.0, 6.8

and 7.4 are generally applicable to any adenovirus formulation within the claimed pH range. As stated above, the antimicrobial activity of chlorobutanol is directly related to its stability. Applicants also note that, contrary to the Examiner's assertion, no other formulations were shown to not have the unexpected results.

Thus, Applicants respectfully submit that any *prima facie* case of obviousness has been rebutted.

Claims 3-8 and 23-28 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao as applied to claims 1 and 21 above, and further in view of Evans et al. (WO 01/66137 A1, "Evans") for reasons of record.

Based on the above, Applicants respectfully submit that the *prima facie* case of obviousness has been rebutted. As Evans fails to remedy the deficiencies of Gao, Applicants respectfully submit that present invention is not obvious over Gao in view of Evans.

Accordingly, for the reasons above, Applicants respectfully submit that rejections under 35 U.S.C. 103(a) have been obviated.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

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